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(71) Applicants and
(72) Inventors: **NILSSON, Ulf** [SE/SE]; Smedsvovägen 10, S-225 94 Lund (SE). **LEFFLER, Hakon** [SE/SE]; Svanegatan 7 B, S-222 24 Lund (SE). **SÖRME, Pernilla** [SE/SE]; Kulgränden 5B167, S-226 49 Lund (SE).

(74) Agents: **AWAPATENT AB** et al.; Box 5117, S-200 71 Malmö (SE).

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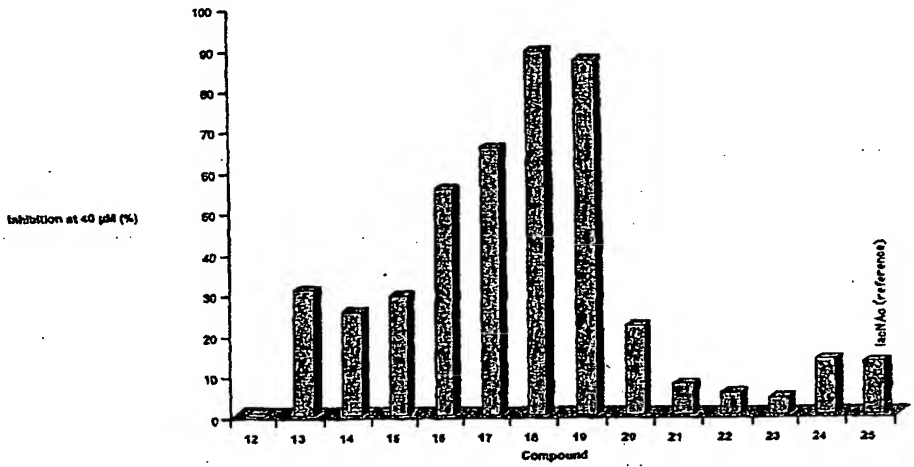
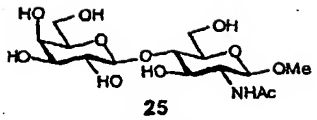
(54) Title: NEW INHIBITORS AGAINST GALECTINS





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(57) Abstract: The present invention relates to novel compounds, the use of said compounds as a medicament as well as for the manufacture of a medicament for treatment of disorders relating to the binding of galectin to receptors in a mammal. Said galectin is preferably a galectin 3.

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NEW INHIBITORS AGAINST GALECTINS

Technical field of the invention

The present invention relates to novel compounds, the use of said compounds as a medicament and for the manufacture of a medicament for the treatment of any disorder relating to the binding of a galectin to receptors in a mammal. The invention also relates to pharmaceutical compositions comprising said novel compounds.

Background Art

The galectins are a family of proteins defined by shared sequence elements and by affinity for β-galactosides (Barondes et al., 1994). There are now ten known mammalian galectins (Fig.1), but biochemical analysis of tissues as well as the accumulation of partial DNA sequences from expressed sequence tags (ESTs) suggest that there are many more (Cooper and Barondes, 1999). Galectins occur at high concentration (usually 0.-1% of total soluble cell protein) in a limited range of cell types, different for each galectin.

All galectins bind lactose and other β-galactosides, but they differ in their affinity for more complex saccharides (Leffler and Barondes, 1986, Barondes et al., 1994). This suggests that galectins may play a role in decoding the information in complex carbohydrates at the cell surface and in the extracellular matrix. A review of the data up to 1999 is given by Leffler (2001). By cross-linking cell-surface and extracellular glycoproteins (e.g. laminin, integrins, and IgE receptors), extracellular galectins are known to modulate cell adhesion and induce intracellular signals. By the adhesion modulation, galectins may play roles in maintenance of tissue integrity and in cancer metastasis. By the signaling activity, galectins may induce a variety of responses including apoptosis in T-lymphocytes,

oxidative burst in neutrophil leukocytes, and through these activities be important in inflammation and immune regulation. In addition, galectins may have intracellular functions; there is evidence for binding to intracellular non-carbohydrate ligands, and roles in RNA splicing and modulation of apoptosis have been suggested.

The best studied are galectin-3 and galectin-1. The present invention relates mainly to galectin-3, but its principles may be applicable also to other galectins.

Potential therapeutic use of galectin-3 inhibitors.

Galectin-3 has been implicated in diverse phenomena and, hence inhibitors may have multiple uses. It is easy to perceive this as a lack of specificity or lack of scientific focus. Therefore, the analogy with aspirin and the cyclooxygenases (COX-I and II) is useful. The COXs produce the precursor of a wide variety of prostaglandins and, hence, are involved in a diverse array of biological mechanisms. Their inhibitors, aspirin and other NSAIDs (non-steroid anti-inflammatory drugs), also have broad and diverse effects. Despite this, these inhibitors are very useful medically, and they have several different specific utilities.

So if galectins, like COXs, are part of some basic biological regulatory mechanism (as yet unknown), they are likely to be 'used by nature' for different purpose in different contexts. Galectin inhibitors, like NSAIDs, are not expected to wipe out the whole system, but to tilt the balance a bit.

Inhibition of inflammation.

There is now ample evidence that galectin-3 is proinflammatory (reviewed by Leffler, 2001). Its expression is induced in macrophages and other cells during inflammation (Perillo et al., 1998). It has various proinflammatory effects on other cells in the inflammatory site (Sano et al., 2000; Karlsson et al., 1998). Galectin-3 gene null-mutant (knock-out) mice have decreased inflammatory responses (Hsu et al., 2000) and

knock-out mice of Mac-2BP, a galectin-3 ligand, have increased inflammatory responses (Trahey et al., 1999). Inflammation is a protective response of the body to invading organisms and tissue injury. However, if unbalanced it also frequently is destructive and occur as part of the pathology in many diseases. Because of this there is great medical interest in pharmacological modulation of inflammation. A galectin-3 inhibitor is expected to provide an important addition to the arsenal available for this.

Treatment of septic shock.

The idea of a possible role of galectin-3 in septic shock comes from our own studies (Almquist et al., 2001). Briefly the argument goes as follows. It is known that septic shock involves dissemination of bacterial lipopolysaccharide into the blood stream, and that the pathological effects of this are mediated via neutrophil leukocytes (Karima et al., 1999). LPS does not activate the tissue damaging response of the neutrophil. Instead it primes the neutrophil, so that it is converted from unresponsive to responsive to other, presumably endogenous, activators. In septic shock this priming happens prematurely in the blood stream. Endogenous activators could then induce the tissue damaging response in the wrong place and time. Several candidates have been proposed as these endogenous activators, including TNF-alfa. Inhibitors of these have been used in treatment schemes without much success (Karima et al., 1999). Since our own studies indicate that galectin-3 is a good candidate as an endogenous activator of primed neutrophils (Almquist et al., 2001), galectin-3 inhibitors may be very useful in septic shock.

Treatment of cancer.

There is a whole other body of evidence suggesting that induced expression of galectin-3 (and perhaps other galectins) promote tumour growth and/or metastasis (reviewed by Leffler, 2001). The evidence is on one hand

correlatory -- more galectin in more malignant tumours. The direct evidence comes from animal models, mainly by Raz et al, but also others. In paired human tumour cell lines (with decreased or increased expression of galectin-3), the one with more galectin-3 gives more tumours and metastasis in nude mice (Bresalier et al., 1998). A polysaccharide, which inhibits galectin-3 can inhibit tumours *in vivo* (Pienta et al., 1995). Although there may be different explanations for the effects of galectin-3, inhibition of its activities is expected to be beneficial in cancer.

Galectin-1 and galectin-9 have been shown to induce apoptosis in activated T-cells. Also, galectin-1 is frequently over-expressed in low differentiated cancer cells, and galectin-9 (or its relatives galectin-4 and galectin-8) is expressed in certain cancer types. Hence, these galectins might help the tumour to defend itself against the immune response raised by the host (Perillo et al., 1998; Leffler, 2001). Inhibitors of the galectin would be expected to block such an effect and thereby be useful in cancer treatment.

Known inhibitors

Natural ligands.

Solid phase binding assays and inhibition assays have identified a number of saccharides and glycoconjugates with the ability to bind galectins (reviewed by Leffler, 2001). All galectins bind lactose with K_d of 0,5 - 1 mM. The affinity of D-galactose is 50 - 100 times lower. *N*-Acetyllactosamine and related disaccharides bind about as well as lactose but for certain galectins up to 10 times better. The best small saccharide ligands for galectin-3 were those carrying blood group A-determinants attached to lactose or lacNAc-residues and were found to bind up to about 50 times better than lactose. Galectin-1 shows no preference for these saccharides.

Larger saccharides of the polylactosamine type have been proposed as preferred ligands for galectins. In

solution using polylactosamine carrying glycopeptides, there was evidence for this for galectin-3 but not galectin-1 (Leffler and Barondes, 1986). A modified plant pectin polysaccharide has been reported to bind galectin-3 (Pienta et al., 1995).

The above described natural saccharides that have been identified as galectin-3 ligands are not suitable for use as active components in pharmaceutical compositions, because they are susceptible to acidic hydrolysis in the stomach and to enzymatic degradation. In addition, natural saccharides are hydrophilic in nature and are not readily absorbed from the gastrointestinal tract following oral administration.

Synthetic inhibitors.

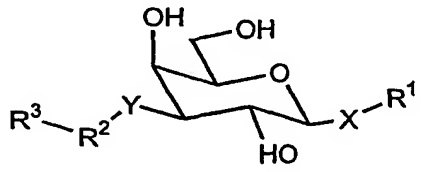
Thiodigalactoside is known to be a synthetic inhibitor approximately as efficient as *N*-acetyllactosamine (Leffler and Barondes, 1986). Saccharides coupled to amino acids with anti-cancer activity were first identified as natural compounds in serum, but subsequently synthetic analogues have been made (Glinsky et al., 1996). Among them, those with lactose or Gal coupled to the amino acid inhibits galectins but only with about the same potency as the corresponding underivatized sugar. A divalent form of a lactosyl-amino acid had higher potency in a solid phase assay (Naidenko et al., 2000). Starburst dendrimers (André et al, 1999) and glycopolymers (Pohl et al, 1999), made polyvalent in lactose-residues, have been described as galectin-3 inhibitors with marginally improved potency as compared to lactose. The aforementioned synthetic compounds that have been identified as galectin-3 ligands are not suitable for use as active components in pharmaceutical compositions, because they are hydrophilic in nature and are not readily absorbed from the gastrointestinal tract following oral administration. Dendrimers and glycopolymers are too large to be absorbed and large enough to produce immune responses in patients.

Furthermore, dendrimers and glycopolymers are susceptible to acidic hydrolysis in the stomach and to enzymatic hydrolysis.

Thus, there is a considerable need within the art of inhibitors against galectin, in particularly to galectin 3.

Summary of the invention

Therefore, the present invention relates to a compound having the general formula (I):



(I)

wherein

the configuration of the pyranose ring is D-galacto;

X is selected from the group consisting of O, S, NH, CH_2, and NR^4, or is a bond;

Y is selected from the group consisting of NH, CH_2, and NR^4, or is a bond;

R^1 is selected from the group consisting of:

a) a saccharide;

b) hydrogen, an alkyl group, an alkenyl group, an aryl group, a heteroaryl group, and a heterocycle;

R^2 is selected from the group consisting of CO, SO_2, SO, PO, and PO_2;

R^3 is selected from the group consisting of;

a) an alkyl group of at least 4 carbon atoms, an alkenyl group of at least 4 carbon atoms, an alkyl or alkenyl group of at least 4 carbon atoms substituted with a carboxy group, an alkyl group of at least 4 carbon atoms substituted with both a carboxy group and an amino group, and an alkyl group of at least 4 carbon atoms substituted with a halogen; or

b) a phenyl group, a phenyl group substituted with a carboxy group, a phenyl group substituted with at least

one halogen, a phenyl group substituted with an alkoxy group, a phenyl group substituted with at least one halogen and at least one carboxy group, a phenyl group substituted with at least one halogen and at least one alkoxy group, a phenyl group substituted with a nitro group, a phenyl group substituted with a sulfo group, a phenyl group substituted with an amine group, a phenyl group substituted with a hydroxy group, a phenyl group substituted with a carbonyl group and a phenyl group substituted with a substituted carbonyl group; or

c) a phenyl amino group;

R^4 is selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, an aryl group, a heteroaryl group, and a heterocycle.

The present invention also relates to a compound according to above mentioned formula for use as a medicament.

Still further the present invention relates to the use of a compound according to above mentioned formula for the manufacture of a medicament for the treatment of any disorder relating to the binding of a galectin to receptors in a mammal.

Yet further the present invention relates to a pharmaceutical composition comprising a compound according to above mentioned formula as active ingredient together with a pharmaceutically acceptable adjuvant, diluent, excepient or carrier.

Yet further the present invention relates to a method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method comprises administering to said mammal an effective amount of a compound according to above mentioned formula.

Still further the present invention relates to a method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method

comprises administering to said mammal an effective amount of a pharmaceutical composition mentioned above

Galectin specificity and structure.

The studies of galectin specificity using inhibition by small natural saccharides mentioned above indicated that all galectins bound lactose, LacNAc and related disaccharides but that galectin-3 bound certain longer saccharides much better (Leffler and Barondes, 1986). These longer saccharides were characterized by having an additional sugar residue added to the C-3 position of Gal in lactose or LacNAc. The X-ray crystal structure of galectins-1 -2 and -3 demonstrated a highly conserved core binding site for lactose and LacNAc with features in agreement with the specificity studies (Lobsanov and Rini, 1997; Seetharaman et al., 1998). In addition an extended groove was found which might accommodate the added sugar residue in the longer saccharides. The shape of this grove varies among galectins suggesting that the same extensions would not be bound equally by the different galectins. The galectin-3 CRD structure with bound LacNAc and the extended binding site indicated is shown in Fig. 2.

Design of galectin inhibitors based on structure and specificity.

The indication of an extended binding site suggested a possible approach to designing synthetic galectin inhibitors. In this the C-3 of Gal in the core binding site would be modified by a range of structural motifs to produce a collection of diverse chemical structures. The compounds would then be tested in a binding assay for galectins to see which addition created enhanced interaction with the galectins and hence would be a more potent inhibitor. In an initial approach the 3-OH of Gal would be replaced with a 3-NH_2 group to facilitate addition of a large array of extensions in a combinatorial chemistry approach. Other routes of derivatization would also be possible.

In the implementation of this strategy the innovative selection of certain chemical additions to the 3'-amino LacNAc, described below, resulted in surprisingly potent inhibitors of galectin-3.

Brief description of the drawings

Fig. 1. Schematic picture of galectins. The typical 15 kDa carbohydrate binding domains are filled and other domains are unfilled or hatched (reviewed by Barondes et al., 1994, and by Leffler, 2001).

Fig. 2. A) Structure of galectin-3 CRD (shown as smooth surface) with bound LacNAc (stick model) and extended binding site indicated (white semitransparent arrow). The structure with bound LacNAc is from Seetharaman et al. (1998). Major interacting amino acid residues are indicated by black arrows and text. Sugar residues are indicated by grey text (Gal = galactose, Nag = N-acetylglucosamine). The white semitransparatnt arrow points through the extended binding site at the 3-OH of Gal which is the site of modification discussed in the present invention. B) Schematic of inhibitors based on the strategy in this invention.

Fig. 3. Screening experiment. Percent inhibition of a Galα3Galβ4GlcNAcβ trisaccharide:horseradish peroxidase conjugate binding to galectin-3 coated microwells at 40 μM inhibitor concentration.

Fig. 4. Determination of IC_{50} values of inhibitors 16, 18, 19 and 25 with competitive inhibition of a Galα3Galβ4GlcNAcβ trisaccharide:horseradish peroxidase conjugate binding to galectin-3 coated microwells.

Detailed description of preferred embodiments of the invention

According to one aspect of the invention a compound of above mentioned formula comprises a saccharide (R^1=saccharide), which sacharide is selected from the group consisting of glucose, mannose, galactose, N-acetylglucosamine, N-acetylgalactosamine, fucose, fructose, xylose, sialic acid, glucoronic acid, iduronic

acid, a disaccharide or an oligosaccharide comprising at least two of the above saccharides, and derivatives thereof. Any other saccharide known to a person skilled within the art may obviously be used as an alternative to the above mentioned saccharides.

In another aspect of the invention, in the above mentioned formula, Y is NH, X is O and said halogen is selected from the group consisting of F, Cl, Br and I. Preferably said halogen is F.

In the present disclosure the term "alkyl group" is meant to comprise from 1 to 12 carbon atoms. Said alkyl group may be straight or branched chain. Said alkyl group may also form a cycle comprising from 3 to 12 carbon atoms.

In the present disclosure the term "alkenyl group" is meant to comprise from 1 to 12 carbon atoms. Said alkenyl group comprises at least one double bond.

In the present disclosure the term "aryl group" is meant to comprise from 4 to 18 carbon atoms. Said aryl group may be a phenyl group or a naphtyl group.

In the present disclosure the term "alkoxy group" is meant to comprise from 1 to 12 carbon atoms. Said alkoxy group may be a methoxy group or an ethoxy group.

In the present disclosure the term "alkylamino group" is meant to comprise from 1 till 12 carbon atoms.

In the present disclosure the term "arylamino group" is meant to comprise from 4 to 12 carbon atoms. Said "arylamino group" may be aniline, carboxylated aniline or halogenated aniline.

In the present disclosure the term "heteroaryl group" is meant to comprise from 4 to 18 carbon atoms, wherein at least one atom of the ring is a heteroatom, i.e. not a carbon. Preferably said heteroatom is N, O or S. Said heteroaryl group may be a pyridine, a pyrrole, a furan or a thiophene.

In the present disclosure the term "heterocycle" is meant to comprise from 1 to 12 carbon atoms in a ring

structure, wherein at least one of the atoms in the ring is a heteroatom, i.e. not a carbon. Preferably said heteroatom is O, S or N.

The above mentioned groups may naturally be substituted with any other known substituents within the art of organic chemistry. The groups may also be substituted with two or more of the substituents. Examples of substituents are halogen, alkoxy, nitro, sulfo, amine, hydroxy, and carbonyl groups.

In yet another aspect of the invetion said compound is methyl 2-acetamido-2-deoxy-4-*O*-(3-[3-carboxypropanamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (14), methyl 2-acetamido-2-deoxy-4-*O*-(3-[{Z}-3-carboxypropenamido]-3-deoxy-β-D-galactopyranosyl)- β-D-glucopyranoside (15), methyl 2-acetamido-2-deoxy-4-*O*-(3-benzamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (16), methyl 2-acetamido-2-deoxy-4-*O*-(3-[2-carboxybenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (17), methyl 2-acetamido-2-deoxy-4-*O*-(3-[4-methoxy-2,3,5,6-tetrafluorobenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (18), methyl 2-acetamido-2-deoxy-4-*O*-(3-[2-carboxy-3,4,5,6-tetrafluorobenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (19), methyl 2-acetamido-2-deoxy-4-*O*-(3-methanesulfonamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (20), methyl 2-acetamido-2-deoxy-4-*O*-(3-[4-nitrobenzenesulfonamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (21), methyl 2-acetamido-2-deoxy-4-*O*-(3-phenylaminocarbonylamino-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (22), methyl 2-acetamido-2-deoxy-4-*O*-(2-aminoacetamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (23), methyl 2-acetamido-2-deoxy-4-*O*-(3-[{2S}-2-amino-3-carboxy-propanamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (24). Preferably said compound is methyl 2-acetamido-2-deoxy-4-*O*-(3-benzamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (16), methyl 2-acetamido-2-deoxy-4-*O*-(3-

[2-carboxybenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (17), methyl 2-acetamido-2-deoxy-4-*O*-(3-[4-methoxy-2,3,5,6-tetrafluorobenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (18), or methyl 2-acetamido-2-deoxy-4-*O*-(3-[2-carboxy-3,4,5,6-tetrafluorobenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (19).

In one aspect the present invention relates to the use of a compound according to above mentioned formula, for the manufacture of a medicament for the treatment of any disorder relating to the binding of a galectin to receptors in a mammal. In one aspect of the invention said galectin is galectin 3.

In another aspect the invention relates to the use of a compound according to above mentioned formula, for the manufacture of a medicament for the treatment of a disorder being selected from the group consisting of inflammation, septic shock, cancer, autoimmune diseases such as reumatoid artrit and multipel schlerosis. Preferably said compound is for the manifacture of a medicament for the treatment of cancer.

In yet another aspect the present invention relates to a pharmaceutical composition comprising a compound according to above mentioned formula as active ingredient together with a pharmaceutically acceptable adjuvant, diluent, excepient or carrier. A pharmaceutical composition of the invention comprises from 1 to 99 weight % of a pharmaceutically acceptable adjuvant, diluent, excepient or carrier and from 1 to 99 weight % of a compound according to above mentioned formula.

In one aspect the invention relates to a method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method comprises administering to said mammal an effective amount of a compound according to above mentioned formula. In one particularly important aspect of the invention said galectin is a galectin 3.

In another aspect the invention relates to a method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method comprises administering to said mammal an effective amount of a pharmaceutical composition according to the above. In one particularly important aspect of the invention said galectin is a galectin 3.

The pharmaceutical composition according to the present invention comprising a compound of the invention may be adapted for oral, intravenous, topical, intraperitoneal, nasal, buccal, sublingual, or subcutaneous administration or for administration via the respiratory tract in the form of e.g. an aerosol or an air-suspended fine powder. Therefore, the pharmaceutical composition of the present invention may be in the form of for example tablets, capsules, powders, solutions, transdermal patches or suppositories.

The pharmaceutical composition of the present invention may optionally comprise two or more compounds of the present invention. The composition may also be used together with other medicaments within the art for treatment of related disorders.

The typical dosages of the compounds of the present invention varies within a wide range and depends on many factors such as the route of administration, the requirement of the individual in need of treatment, the individuals body weight, age and general condition.

The adjuvants, diluents, excepients and/or carriers that may be used in the composition of the invention must be pharmaceutically acceptable in the sense of being compatible with the compounds and the other ingredients of the pharmaceutical composition and not deleterious to the recipient thereof. The adjuvants, diluents, excepients and carriers that may be used in the pharmaceutical composition of the invention are well known to a person within the art.

Definitions

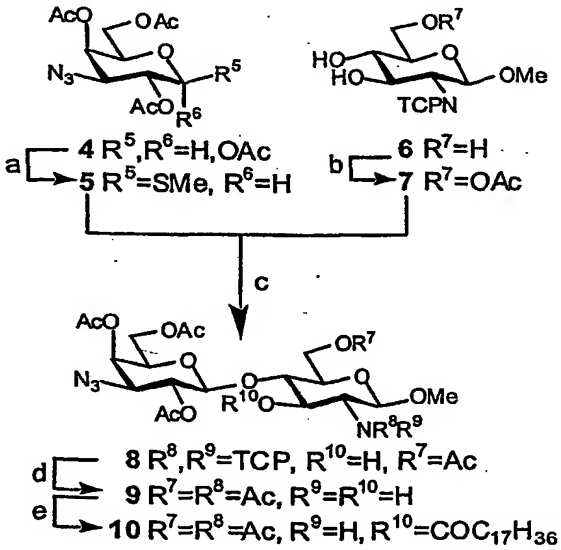
IC_{50} : Inhibitor concentration that causes 50% inhibition of galectin-3 activity in a defined assay below.

K_{rel} : Ratio of IC_{50}value of the reference compound methyl 4-*O*-β-D-galactopyranosyl-2-acetamido-2-deoxy-β-D-glucopyranoside 25 and of IC_{50}value of an inhibitor.

$\Delta\Delta G$: $-RTlnK_{rel}$ (kJ/mol)

Synthesis of the starting material

As starting material for the synthesis of novel 3'-amino derivatives of *N*-acetyllactosamine 12-24 was used methyl 4-*O*-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-stearoyl-β-D-glucopyranoside 10, which was prepared from 1,2,4,6-tetra-*O*-acetyl-3-azido-3-deoxy-D-galactopyranose 4 (Lowary and Hindsgaul, 1994) and methyl 2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside 6 (Stangier and Hindsgaul, 1996) following methods well known to one skilled in the art (Scheme 1). Compound 10 carries a masked 3'-amino group in the form of an azide, as well as a 3-*O*-stearoyl group to allow purification with C18 solid-phase extraction.



Scheme 1

Scheme 1. a) $MeSSiMe_3$,TMSOTf, $(CH_2Cl)_2$, 7 days, 86%. b) AcCl, *s*-collidine, CH_2Cl_2, -20° C, 7 h, 75%. c) NIS, TfOH,

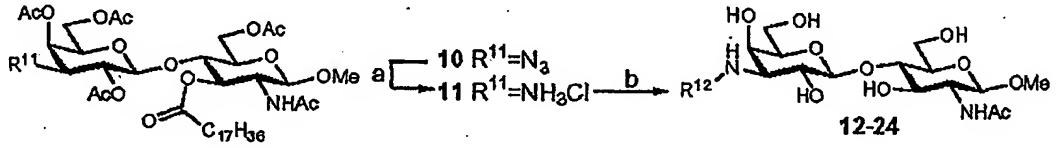
CH_2Cl_2, MS AW-300, -42° C, 2 h, 75%. d) $^{i}H_2N(CH_2)_2NH_2$, EtOH, 60° C, 7.5 h, then ^{ii}MeOH, H_2O, Ac_2O, 12 h, 83%. e) $C_{17}H_{36}COCl$, DMAP, Pyridine, CH_2Cl_2, 24 h, 80%.

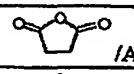
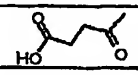
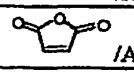
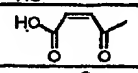
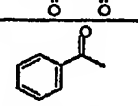
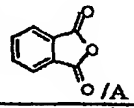
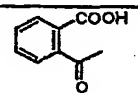
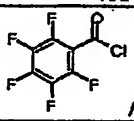
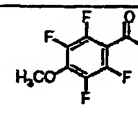
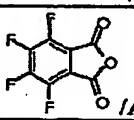
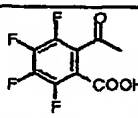
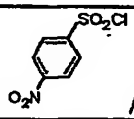
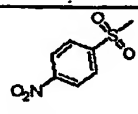
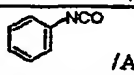
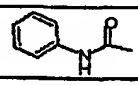
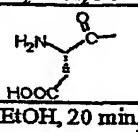
Synthesis of the 3-amino derivatives of N-acetyllactosamine 12-24.

Reduction of the azido group in methyl 4-*O*-(2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-stearoyl-β-D-glucopyranoside 10 was accomplished by catalytic hydrogenation in ethanol/HCl over Pd/C to give methyl 4-*O*-(2,4,6-tri-*O*-acetyl-3-amino-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-*O*-acetyl-2-deoxy-3-*O*-stearoyl-β-D-glucopyranoside 11, which was immediately treated with reagents for amide, sulfonamide and urea formation using methods well known to one skilled in the art (Table 1). Removal of protecting groups according to methods well known to those skilled in the art yielded the 3'-amino derivatives of *N*-acetyllactosamine 12-24.

TABLE 1. Parallel synthesis and spectroscopic data of 3'-amino *N*-acetyl-lactosamine library (12-24).

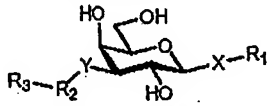
TABLE 1. Parallel synthesis and spectroscopic data of 3'-amino *N*-acetyl-lactosamine library (12-24).

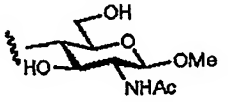
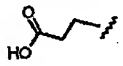
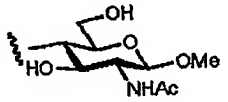
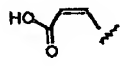
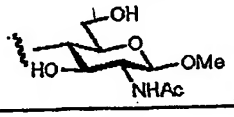
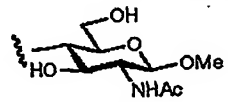
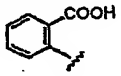
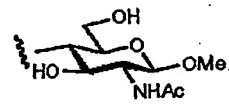
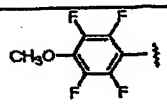
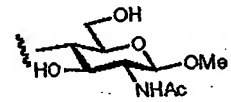
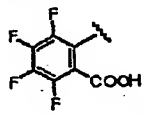
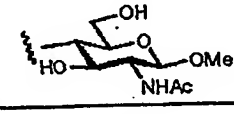
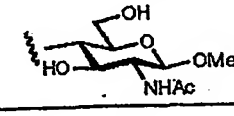
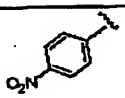
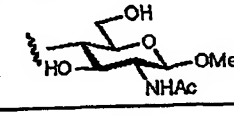
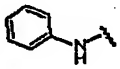
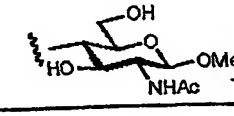
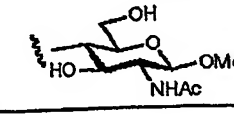


	Reagent/Conditions[b]	R^{12}=	Yield (%)	^{1}H-NMR data (400MHz, D_2O) δ	HRMS[c] Calcd/Found
12	None/A[ii](Helland et al. 1995)	H–	59	4.60 (d,1H, J=8.8 Hz, H-1), 4.48 (d,1H, J=8.3 Hz, H-1)	397.1822/ 397.1824
13	Ac_2O/A	Ac–	79	4.58 (d, 1H, *J*=7.8 Hz, H-1'), 4.48 (d, 1H, *J*= 7.7 Hz, H-1), 2.07, 2.05 (2s, 3H each, NAc)	461.1747/ 461.1750
14	 /A		100	4.58 (d, 1H, *J*=7.8 Hz, H-1'), 4.48 (d, 1H, *J*=7.9 Hz, H-1), 2.55 (m, 2H, CH_2), 2.48 (m, 2H, CH_2)	519.1802/ 519.1802
15	 /A		32	6.37 and 6.12 (2d, 1H each, *J*=12.3 Hz, CH), 4.59 (d, 1H, *J*=7.7 Hz,H-1'), 4.47 (d, 1H, *J*=7.7 Hz, H-1)	517.1646/ 517.1659
16	BzCl/A		24	7.83-7.54 (m, 5H, Ar), 4.65 (d, 1H, *J*=7.7 Hz, H-1'), 4.49 (d, 1H, *J*=7.9 Hz, H-1)	523.1904/ 523.1909
17	 /A		70	7.67-7.51 (m, 4H, Ar), 4.65 (d, 1H, *J*=7.8 Hz, H-1'), 4.48 (d, 1H, *J*=8.1 Hz, H-1)	567.1802/ 567.1802
18	 /A		83	4.64 (d, 1H, *J*=7.9 Hz, H-1'), 4.49 (d, 1H, *J*=7.9 Hz, H-1)	625.1633/ 625.1652[d]
19	 /A		62	4.63 (d, 1H, *J*=7.7 Hz, H-1'), 4.80 (d, 1H, J=7.0 Hz, H-1)	661.1245/ 661.1243
20	CH_3SO_2Cl/A	CH_3SO_2-	10	4.55 (d, 1H, *J*=6.8 Hz,H-1'), 4.47 (d, 1H, *J*=8.0 Hz, H-1), 3.16 (s, 3H, Me)	497.1417/ 497.1415
21	 /A		7	8.42 (d, 2H, *J*=8.9 Hz, Ar), 8.13 (d, 2H, *J*=8.5 Hz, Ar-H), 4.45 (d, 1H, J=7.8 Hz, H-1), 4.44 (d, 1H, J=7.2 Hz, H-1')	604.1424/ 604.326[e]
22	 /A		15	7.43-7.99 (m, 5H, Ar), 4.61 (d, 1H, *J*=7.8 Hz, H-1'), 4.48 (d, 1H, *J*=7.8 Hz, H-1)	538.2013/ 538.2022
23	*N*-*t*Boc-glycine/B	H_2NCH_2CO-	68	4.59 (d, 1H, *J*=7.4 Hz, H-1'), 4.47 (d, 1H, *J*=8.1 Hz, H-1)	476.1856/ 476.1855
24	*N*-*t*Boc-L-aspartic acid β-*t*butyl ester/B		9	4.59 (d, 1H, J=7.5 Hz, H-1), 4.48 (d, 1H, J=8.4 Hz, H-1')	534.1911/ 534.543[d]

[a]10% Pd/C, H_2 (1 atm.), HCl, EtOH, 20 min.
[b]A: [i]pyridine, CH_2Cl_2. [ii]NaOMe/MeOH. B: [i]DIC, CH_2Cl_2. [ii]TFA, CH_2Cl_2. [iii]NaOMe/MeOH.
[c]$(M+Na)^+$, except for **12** $(M+H)^+$ and **19** $(M-H+2Na)^+$.
[d]NaOMe treatment substituted one fluoro with one methoxy group
[e]MALDI-TOF MS

TABLE 2. Relationship between compounds 14-24 and the general structure in claim 1:



	X	Y	R^1	R^2	R^3
14	O	NH		CO	
15	O	NH		CO	
16	O	NH		CO	
17	O	NH		CO	
18	O	NH		CO	
19	O	NH		CO	
20	O	NH		SO_2	CH_3—
21	O	NH		SO_2	
22	O	NH		CO	
23	O	NH		CO	H_2NCH_2—
24	O	NH		CO	

Screening against galectin-3.

Compounds 12-24 were screened for efficiency in inhibiting galectin-3 binding to a natural receptor (Figure 3). Compounds 16-19 containing different 3'-benzamide functionalities, showed unexpected high efficiency (55-89% inhibition at 40 μM) as compared to the known reference inhibitor methyl 4-*O*-β-D-galactopyranosyl-2-acetamido-2-deoxy-β-D-glucopyranoside 25 (13% inhibition at 40 μM). Other inhibitors were similar (0.7-30% inhibition at 40 μM) to the reference 25. These results were confirmed in an unrelated assay based on fluorescence polarization.

Determination of IC_{50} values.

IC_{50} values of the three best inhibitors, 16, 18-19, identified from screening experiments, and the reference inhibitor 25 were determined by inhibition of galectin-3 with serial dilutions of the inhibitors (Figure 4). Fluorinated benzamides were up to 41 times as efficient as the known reference inhibitor 25. Compound 18 has an IC_{50} value of 4.8 μM, which is unprecedented in the field of monovalent galectin-3 inhibitors (Table 3). X-Ray crystallography of the galectin-3:18 complex show that the increased affinity for 18 originates in a stacking interaction between the fluorinated benzamide group at C-3' of 18 and arg144 of galectin-3. This beneficial stacking interaction is enabled by an unpredictable move of the arg-144 side-chain by approximately 2.6 Å, as compared to the parent reference galectin-3:25 complex. The unexpectedly high inhibitor potency of 16-19 against galectin-3 renders them suitable as active components in pharmaceutical compositions targeting conditions where galectin-3 plays a pathogenic role. In addition, the unnatural substitutents at C-3 of the galactose residue of compounds 16-19 are expected to improve hydrolytic stability and to improve absorption in the gastro-intestinal tract.

Table 3

	IC_{50} (μM)	K_{rel}
16	23	9
18	4.8	41
19	11.2	18
25	199	1

Methodology/Experimental

General synthetic procedures

The compounds of this invention may be prepared by the following general methods and procedures. The galectin-3 assays of this invention may be performed by the following general methods and procedures. It should be appreciated that where typical or preferred process conditions (e.g. reaction temperatures, times, molar ratios of reactants, solvents, pressures, pH etc) are given, other process conditions may also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants, solvents used and pH etc., but such conditions can be determined by one skilled in the art by routine optimization procedures.

NMR-spectra were recorded with a Bruker DRX-400 instrument. Chemical shifts are given in ppm, with reference to internal $CHCl_3$ (δ 7.26 ppm) or HDO (δ 4.81 ppm). Chemical shifts and coupling constants were obtained from ^{1}H-NMR and proton resonances were assigned from COSY experiments. High-resolution FAB mass spectra (HRMS) were recorded with a JEOL SX-120 instrument. MALDI-TOF Spectra were recorded with a Bruker, Biflex instrument. Column chromatography was performed on SiO_2 (Matrex, 60 Å, 35-70 μm, Grace Amicon) and TLC was carried out on SiO_2 60 F_{254} (Merck) with detection under UV light and developed with aqueous sulfuric acid. Concentrations were made using rotary evaporation with bath temperature at or below 40° C. CH_2Cl_2 and CH_3CN were dried by distillation from CaH_2. Pyridine was dried over 4 Å molecular sieves. DMF was distilled and dried over 4 Å molecular sieves. MeOH and EtOH were dried over 3Å

molecular sieves. Microwell plates were from Nalge Nunc International (Nunc-immuno plate, maxisorp surface). PBS containing 0.05% Tween 20 is abbreviated PBS-T and PBS-T containing 1% BSA is abbreviated PBSA-T. Recombinant human galectin-3 was produced in *Escherichia coli* and purified as previously described (S.M. Massa et al, 1993). The Galα3Galβ4GlcNAcβ-HRP conjugate (HRP-2) was from Glycorex AB, LUND, SWEDEN. Microwell plates were developed with a TMB-peroxidase substrate kit (BioRad 172-1066) according to the manufacturers recommendations.

Synthesis of starting material 10 (Scheme 1).

Methyl 3-azido-3-deoxy-2,4,6-tri-O-acetyl-1-thio-β-D-galactopyranoside (5). To a solution of 4 (Lowary and Hindsgaul, 1994) (231 mg, 0.619 mmol), (methylthio)trimethylsilane (0.250 mL, 1.76 mmol), and molecular sieves AW-300 (0.46 g) in 1,2-dichloroethane (3.0 mL) was added trimethylsilyltriflouromethane sulfonate (0.102 mL, 0.564 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 7 days, aqueous Na_2CO_3 (5%, 5 mL) was added, and the mixture was stirred for another 2 hours. The organic layer was separated, washed with water, dried over Na_2SO_4, filtered, and concentrated. The residue was chromatographed (SiO_2, 2:1 heptane-ethylacetate) to give 5 (192 mg, 86%), $[\alpha]_D^{25}$ -34.8° (c 1.0, $CHCl_3$). ^{1}H-NMR data (400MHz, $CDCl_3$) δ5.45(dd, 1H, *J*=3.4, 1.2 Hz, H-4), 5.22 (t, 1H, *J*=10.0 Hz, H-2), 4.36 (d, 1H, *J*=9.8 Hz, H-1), 4.15-4.07 (m, 2H, H-6, 6´), 3.91 (dt, 1H, *J*=6.6, 1.2 Hz, H-5), 3.66 (dd, 1H, *J*=10.2, 3.4 Hz, H-3), 2.19, 2.17, 2.15 (3 s, 3H each, Ac), 2.06 (s, 3H, Me). HRMS calc. for $C_{13}H_{19}N_3NaO_7S$ (M+Na): 384.0841; found: 384.0837.

Methyl 6-O-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (7). To compound 6 (Stangier and Hindsgaul, 1996) (653 mg,1.42 mmol) and *sym*-collidine (0.940 mL, 7.09 mmol) in CH_2Cl_2 (25 mL) under nitrogen atmosphere at -42° C, was added dropwise acetyl chloride (0.115 mL, 1.62 mmol). The reaction was continued at -20°

C for 4 hours, then additional acetyl chloride (0.025 mL, 0.352 mmol) and *sym*-collidine (0.400 mL, 3.0 mmol) were added. The reaction was quenched with MeOH (8ml) after 3 more hours. The reaction mixture was partitioned between CH_2Cl_2 and aqueous HCl (0.5 M). The organic layer was neutralized with aqueous saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was chromatographed (SiO_2, 1:1 heptane-ethylacetate) to give 7 (535 mg, 75%), $[\alpha]_D^{25}$ -18.4° (c 1.0, $CHCl_3$). ^{1}H-NMR data (400MHz, $CDCl_3$), δ 5.04 (d, 1H, *J*=8.5 Hz, H-1), 4.45 (dd, 1H, *J*=11.9, 2.2 Hz, H-6), 4.27 (dd, 1H, *J*=11.9, 5.5 Hz, H-6´), 4.19 (dd, 1H, *J*=10.7, 8.7 Hz, H-3), 3.93 (dd, 1H, *J*=10.7, 8.5 Hz, H-2), 3.63-3.58 (m, 1H, H-5), 3.44-3.41 (m, 1H, H-4), 3.39 (s, 3H, O_{Me}), 2.09 (s, 3H, Ac). HRMS calc. for $C_{17}H_{15}Cl_4NNaO_8$ (M+Na): 523.9449; found: 523.9447.

Methyl 4-O-(2,4,6-tri-O-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-6-O-acetyl-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside (8). Compounds 5 (66.1 mg, 0.183 mmol), 7 (76.9 mg, 0.153 mmol), and activated molecular sieves AW-300 (0.35 g) were stirred in dry CH_2Cl_2 (5.0 mL) for 30 minutes with under nitrogen atmosphere. The mixture was cooled to -42° C and *N*-iodosuccinimide (51.2 mg, 0.228 mmol) was added followed by trifluoromethanesulfonic acid (2.0 μL, 22.6 μmol). The reaction mixture was allowed to reach room temperature after 2 hours, filtered, and diluted with CH_2Cl_2. The organic layer was washed with 10% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, 2:1 heptane-ethylacetate) to give 8 (93.9 mg, 75 %), $[\alpha]_D^{25}$ +7.6° (c 1.0, $CHCl_3$). ^{1}H-NMR data (400MHz, $CDCl_3$) δ5.36(d, 1H, *J*=3.1 Hz, H-3), 5.15 (q, 1H, *J*=10.6, 7.9 Hz, H-2), 5.10 (d, 1H, *J*=8.5 Hz, H-1´), 4.52 (d, 1H, *J*=7.9 Hz, H-1), 4.35-4.29 (m, 1H, H-3´), 4.28 (d, 1H, *J*=1.3 Hz, H-4´), 4.06-4.14 (m, 3H, H-6,2´,6´), 3.88-3-99 (m, 2H, H-5, 6), 3.70 (m, 1H, H-5´), 3.59 (q, 1H, *J*=10.6, 3.4 Hz, H-3), 3.53 (d, 1H, *J*=8.2 Hz, H-6´), 3.42

(s, 3H, OMe), 2.15, 2.13, 2.12, 1.90 (4 s, 3H each, Ac). HRMS calc. for $C_{29}H_{30}Cl_4N_4NaO_{15}$ (M+Na): 837.0359; found: 837.0374.

Methyl (2,4,6-tri-O-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-O-acetyl-2-deoxy-β-D-glucopyranoside (9). Dry diaminoethane (18 µL) was added to a solution of 8 (133 mg, 0.152 mmol) in dry EtOH (13 mL). The mixture was heated at 60° C for 7.5 hours then co-concentrated with toluene (5 mL). The residue was dissolved in MeOH (15 mL), H_2O (3 mL), and Ac_2O (4.5 mL), stirred over night, then co-concentrated with toluene (20 mL). The residue was chromatographed (SiO_2, 1:1 toluene-acetone) to give 9 (70.6 mg, 83%), $[\alpha]_D^{25}$ +1.6° (c 0.03, $CHCl_3$). ^{1}H-NMR data (400MHz, $CDCl_3$) δ (d, 1H, *J*= 7.8 Hz, NH), 5.40 (d, 1H, *J*=3.3 Hz, H-4´), 5.17 (dd, 1H, *J*= 10.6, 8.0 Hz, H-2´), 4.62 (d, 1H, *J*= 8.3 Hz, H-1), 4.54 (d, 1H, *J*= 8.0 Hz, H-1´), 4.34-4.31 (m, 2H, OH, H-6), 4.18 (dd, 1H, *J*= 10.7, 3.7 Hz, H-6´), 4.09-3.93 (m, 4H, H-6, 5´, 3, 6´), 3.62-3.57 (m, 2H, H-5,3´), 3.48 (s, 3H, OMe), 3.51-3.44 (m, 2H, H-4,2), 2.17, 2.16, 2.11, 2.06, 2.01 (5 s, 3H each, Ac). HRMS calc. for $C_{23}H_{34}N_4NaO_{14}$ (M+Na): 613.1969; found: 613.1972.

Methyl 4-O-(2,4,6-tri-O-acetyl-3-azido-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-O-acetyl-2-deoxy-3-O-stearoyl-β-D-glucopyranoside (10). To a solution of 9 (65.9 mg, 0.112 mmol), pyridine (0.45 mL) and DMAP (cat.) in dry CH_2Cl_2 (10 mL) under nitrogen atmosphere, was added stearoyl chloride (0.160 mL, 0.475 mmol) at -78° C. The mixture was allowed to reach room temperature, then quenched with EtOH (2 mL) after 24 hours and concentrated. The residue was chromatographed (SiO_2, 3:1 toluene-acetone) to give 10 (75.8 mg, 79%), $[\alpha]_D^{25}$ -16.4° (c 1.0, $CHCl_3$). ^{1}H-NMR data (400MHz, $CDCl_3$) δ 5.72 (d, 1H, *J*=9.5 Hz, NH), 5.39 (d, 1H, *J*= 3.3 Hz, H-4´), 5.07-5.02 (m, 2H, H-2´,3), 4.46 (dd, 1H, *J*=11.9, 8.9 Hz, H-6), 4.44 (d, 1H, *J*=7.9 Hz, H-1´), 4.33 (d, 1H, *J*=7.2 Hz, H-1), 4.19 (dd, 1H, *J*=11.9, 5.4 Hz, H-6), 4.08-4.03 (m, 3H, H-

2, 6´, 6´), 3.85-3.82 (m, 1H, H-5´), 3.74 (t, 1H, *J*=8.1 Hz, H-4), 3.66-3.61 (m, 1H, H-5´), 3.58 (dd, 1H, *J*=10.6, 3.4 Hz, H-3´), 3.44 (s, 3H, OMe), 2.28 (t, 2H, J=7.6 Hz, $-COCH_2-$), 2.14, 2.12, 2.11, 2.06, 1.95 (5 s, 3H, Ac), 1.51-1.64 (m, 2H, $-COCH_2\underline{CH_2}-$), 1.23 (bs, 28H, $-CH_2-$), 0.88-0.85 (m, 3H, CH_3). HRMS calc. for $C_{41}H_{68}N_4NaO_{15}$ (M+Na): 879.4579; found: 879.4596.

Synthesis of inhibitors 12-24 (Table 1 above).

The galectin-3 inhibitors 12-24 of this invention are typically prepared by reaction of a methyl 4-*O*-(2,4,6-tri-*O*-acetyl-3-amino-3-deoxy-β-D-galactopyranosyl)-2-acetamido-6-O-acetyl-2-deoxy-3-O-stearoyl-β-D-glucopyranoside 11 with carboxylic acid halides, anhydrides, sulfonyl halides, isocyanates or amino acid derivatives according to examples A and B below:

Example A:

Typical procedure for acylations and sulfonylations (Synthesis of compounds 12-22). To a solution of 10 (29.0 mg, 38.8 μmol) in EtOH (degassed, 20 mL), was added 1M HCl (0.34 mL, 0.34 mmol) and Pd/C (10%, 33.5 mg). The mixture was hydrogenated (H_2, 1 atm) for 20 minutes, filtered through Celite, and concentrated without heating to give the crude intermediate amine 11, which was immediately used without further purification. The crude 11 was dissolved in dry CH_2Cl_2 (10 mL). Pentafluorobenzoyl chloride (49 μL, 0.34 mmol) and pyridine (15 μL, 0.19 mmol) were added under nitrogen atmosphere. The reaction was monitored by TLC and the reaction mixture was concentrated when 11 was consumed. The residue was dissolved in 70% MeOH and applied onto C18 silica (3 g). Excess reagents and impurities were washed away with 70% MeOH, whereafter elution with 100% MeOH gave a protected intermediate (31.2 mg, 90%) after concentration. The residue was dissolved in MeOH (4.0 mL) and 1 M NaOMe (0.6 mL) was added. The reaction was continued overnight and then neutralized with Duolite C436 (H^+) resin, filtered, and concentrated. The residue was dissolved in water and

applied onto C18 silica (3 g). Excess reagents and impurities were washed away with water, whereafter elution with 30% MeOH gave 18 (16.5 mg, 92%). The products were characterized with ^{1}H-nmr spectroscopy, MALDI-TOF and HRMS-FAB mass spectrometri (Table 1).

Example B:

Typical procedure for acylation with amino acids (Synthesis of compounds 23 and 24). To a solution of 10 (11.3 mg, 13.2 μmol) in EtOH (degassed, 20 mL), was added 1M HCl (0.135 mL, 0.135 mmol) and Pd/C (10%, 12.0 mg). The mixture was hydrogenated (H_2, 1 atm) for 20 minutes, filtered through Celite, and concentrated without heating to give the crude intermediate amine 11, which was immediately used without further purification. A solution of *N*-Boc-glycine (9.0 mg, 51.4 μmol) in dry CH_2Cl_2 (8 mL) was added to the crude 11 under nitrogen atmosphere, followed by *N,N´*-diisopropylcarbodiimide (10 μL, 64.6 μmol) and pyridine (15 μL, 0.19 mmol). The reaction was kept at room temperature overnight then co-concentrated with toluene under reduced pressure. The residue was dissolved in 70% MeOH and applied onto C18 silica (3 g). Excess reagents and impurities were washed away with 70% MeOH, whereafter elution with 100% MeOH gave a protected intermediate (13.1 mg, quantitative) after concentration. To the residue in dry CH_2Cl_2 (5.0 mL) was added TFA (0.5 mL). The reaction was co-concentrated with toluene (15 mL) after 5 hours and the residue was purified by C-18 solid-phase extraction as described above. The residue was dissolved in MeOH (4.0 mL) and NaOMe (0.6 mL, 1 M) was added and the reaction was left overnight, neutralized with Amberlite IR-120 (H^+) resin, filtered, and concentrated. The residue was dissolved in water and applied onto C18 silica (3 g) and elution with water gave 23 (4.1 mg, 84%). The products 23 and 24 were characterized with ^{1}H-nmr spectroscopy, MALDI-TOF and HRMS-FAB mass spectrometry (Table 1).

Inhibition of galectin-3 binding to Galα3Galβ4GlcNAcβ-HRP conjugate

The compounds prepared above (12-24) were tested for their ability to inhibiting the binding of galectin-3 to a Galα3Galβ4GlcNAcβ trisaccharide:horseradish peroxidase conjugate.

Screening experiments. Microtiter plate wells were coated with recombinant galectin-3 (10 µg/ml, 50 µl/well) from *E. coli* at 4° C overnight, then washed three times with PBS-T. The wells were blocked with PBSA-T (100 µl/well) for 1 hour at room temperature, followed by washing with PBS-T. Compounds 12-25 (100 µL/well, 0.2 and 0.04 mM in PBS-T) were added in duplicate to the wells, followed by Galα3Galβ4GlcNAcβ-HRP conjugate (100 µL/well, 1 mg/mL in PBSA-T). The wells were washed with PBS-T after 1 hour incubation at room temperature, followed by development with the TMB-peroxidase substrate kit. The reaction was stopped after 60 min by addition of 1N sulfuric acid (100 µL/well) and optical density was read at 450 nm. Each experiment was conducted twice with each sample in duplicate. The pH of all the compound stock solutions were checked before testing and were all shown to be 7.1.

IC_{50} determinations for compounds 16, 18-19 and 25. Microtiter plate wells were coated with recombinant galectin-3 (10 µg/ml, 50 µl/well) from *E. coli* at 4° C overnight, then washed three times with PBS-T. The wells were blocked with PBSA-T (100 µl/well) for 1 hour at room temperature, followed by washing with PBS-T. To the first well was added 125 µL of inhibitors 16, 18-19 and 25 (0.2 mM in PBS-T). A five-fold serial dilution was performed by transfering 25 µL from the first well to a second well containing 100 µL PBS-T, mixing, then transfering 25 µL from the second well to a third well also containing 100 µL PBS-T, and so on to the eight well from which 25 µL were discarded. The dilution series was done in duplicate. Only PBS-T (100 µL) was added to one column of wells (in order to give the OD in the absence of

inhibitor), as well as to one column of well not coated with galectin-3 (in order to give the background signal). To each well was then added Galα3Galβ4GlcNAcβ-HRP conjugate (100 μL/well, 1 mg/mL in PBS-T). Incubation, washing, and detection was performed as described above. The data was analyzed with non-linear regression analysis using the program Kaleidagraph™ from Synergy Software.

The results of this assay evidenced that the compounds 16-19 inhibited binding of galectin-3 to Galα3Galβ4GlcNAcβ-HRP conjugate with IC_{50}-values less than 50 μM.

From the foregoing description, various modifications and changes in the composition and method will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

Examples of the *in vivo* efficacy of galectin-3 inhibition in inflammation and cancer.

Inflammation.

As mentioned above many studies suggest a role of galectin-3 in enhancing the inflammatory response. For example the addition of galectin-3 to neutrophil leukocytes from an inflammatory site, or primed by exposure to LPS, results in increased generation of toxic oxygen radicals. Lactose can inhibit this response (Karlsson et al., 1998; Almquist et al., 2001). In another study (Sano et al., 2000), galectin-3 was found to be chemotactic to macrophages and monocytes both *in vitro* and *in vivo*. Either lactose or the isolated CRD of galectin-3 (galectin 3C), able to bind the same saccharide receptor as galectin-3 but not cross link it (see below), acted as inhibitors of this response. The substances described in the present invention would be much more effective as inhibitors of the above mentioned responses than lactose because they are much more potent galectin-3 inhibitors. They would also be much more usable *in vivo* than lactose and the galectin-3C because

they are small molecules, more hydrophobic and probably more stable to degradation.

Cancer.

As mentioned above, several studies of models of human cancer in mice indicate that enhanced expression of galectin-3 results in faster tumor growth and more metastasis (Bresalier et al., 1998; reviewed by Leffler, 2001). Injection of a saccharide with inhibitory potency to galectin-3, but perhaps also other proteins, was reported to diminish prostate cancer in rat (Pienta et al., 1995). Hence, potent small molecule inhibitors of galectin-3 are expected to have similar anticancer effects as galectin-3C.

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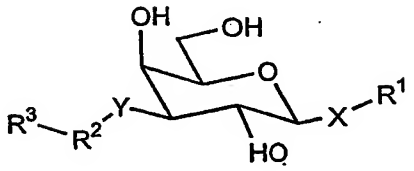
CLAIMS

1. A compound having the general formula (I):



(I)

wherein

the configuration of the pyranose ring is D-galacto;

X is selected from the group consisting of O, S, NH, CH_2, and NR^4, or is a bond;

Y is selected from the group consisting of NH, CH_2, and NR^4, or is a bond;

R^1 is selected from the group consisting of:

c) a saccharide;

d) hydrogen, an alkyl group, an alkenyl group, an aryl group, a heteroaryl group, and a heterocycle;

R^2 is selected from the group consisting of CO, SO_2, SO, PO, and PO_2;

R^3 is selected from the group consisting of;

a) an alkyl group of at least 4 carbon atoms, an alkenyl group of at least 4 carbon atoms, an alkyl or alkenyl group of at least 4 carbon atoms substituted with a carboxy group, an alkyl group of at least 4 carbon atoms substituted with both a carboxy group and an amino group, and an alkyl group of at least 4 carbon atoms substituted with a halogen; or

b) a phenyl group, a phenyl group substituted with a carboxy group, a phenyl group substituted with at least one halogen, a phenyl group substituted with an alkoxy group, a phenyl group substituted with at least one halogen and at least one carboxy group, a phenyl group substituted with at least one halogen and at least one alkoxy group, a phenyl group substituted with a nitro group, a phenyl group substituted with a sulfo group, a

phenyl group substituted with an amine group, a phenyl group substituted with a hydroxy group, a phenyl group substituted with a carbonyl group and a phenyl group substituted with a substituted carbonyl group; or

c) a phenyl amino group;

R^4 is selected from the group consisting of hydrogen, an alkyl group, an alkenyl group, an aryl group, a heteroaryl group, and a heterocycle.

2. A compound according to claim 1, wherein said saccharide (R^1) is selected from the group consisting of glucose, mannose, galactose, N-acetylglucosamine, N-acetylgalactosamine, fucose, fructose, xylose, sialic acid, glucoronic acid, iduronic acid, a disaccharide or an oligosaccharide comprising at least two of the above saccharides, and derivatives thereof.

3. A compoound according to claim 1 or 2, wherein Y is NH.

4. A compound according to any one of claims 1-3, wherein X is O.

5. A compound according to any one of claims 1-4, wherein said halogen is selected from the group consisting of F, Cl, Br and I.

6. A compound according to any one of claims 1-5, wherein said compound is methyl 2-acetamido-2-deoxy-4-O-(3-[3-carboxypropanamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (14), methyl 2-acetamido-2-deoxy-4-O-(3-[{Z}-3-carboxypropenamido]-3-deoxy-β-D-galactopyranosyl)- β-D-glucopyranoside (15), methyl 2-acetamido-2-deoxy-4-O-(3-benzamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (16), methyl 2-acetamido-2-deoxy-4-O-(3-[2-carboxybenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (17), methyl 2-acetamido-2-deoxy-4-O-(3-[4-methoxy-2,3,5,6-tetrafluorbenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (18), methyl 2-acetamido-2-deoxy-4-O-(3-[2-carboxy-3,4,5,6-tetrafluorbenzamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (19), methyl 2-

acetamido-2-deoxy-4-*O*-(3-methanesulfonamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (20), methyl 2-acetamido-2-deoxy-4-*O*-(3-[4-nitrobenzenesulfonamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (21), methyl 2-acetamido-2-deoxy-4-*O*-(3-phenylaminocarbonylamino-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (22), methyl 2-acetamido-2-deoxy-4-*O*-(3-aminoacetamido-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (23), methyl 2-acetamido-2-deoxy-4-*O*-(3-[{2S}-2-amino-3-carboxy-propanamido]-3-deoxy-β-D-galactopyranosyl)-β-D-glucopyranoside (24).

7. A compound according to any one of claims 1-6, for use as a medicament.

8. Use of a compound according to any one of claims 1-6, for the manufacture of a medicament for the treatment of any disorder relating to the binding of a galectin to receptors in a mammal.

9. Use according to claim 8, wherein said galectin is galectin 3.

10. Use according to claim 8 or 9, wherein said disorder is selected from the group consisting of inflammation, septic shock, cancer, autoimmune diseases, reumatoid artrit and multipel schlerosis.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-6 as active ingredient together with a pharmaceutically acceptable adjuvant, diluent, excepient or carrier.

12. A pharmaceutical composition according to claim 11, comprising from 1 to 99 weight % of a pharmaceutically acceptable adjuvant, diluent, excepient or carrier and from 1 to 99 weight % of a compound according to any one of claims 1-6.

13. A method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method comprises administering to said mammal an effective amount of a compound according to any one of claims 1-6.

14. A method for inhibiting conditions associated with the binding of galectin to receptors in a mammal which method comprises administering to said mammal an effective amount of a pharmaceutical composition according to claim 11 or 12.

15. A method according to claim 13 or 14, wherein said galectin is galectin 3.

Fig. 1

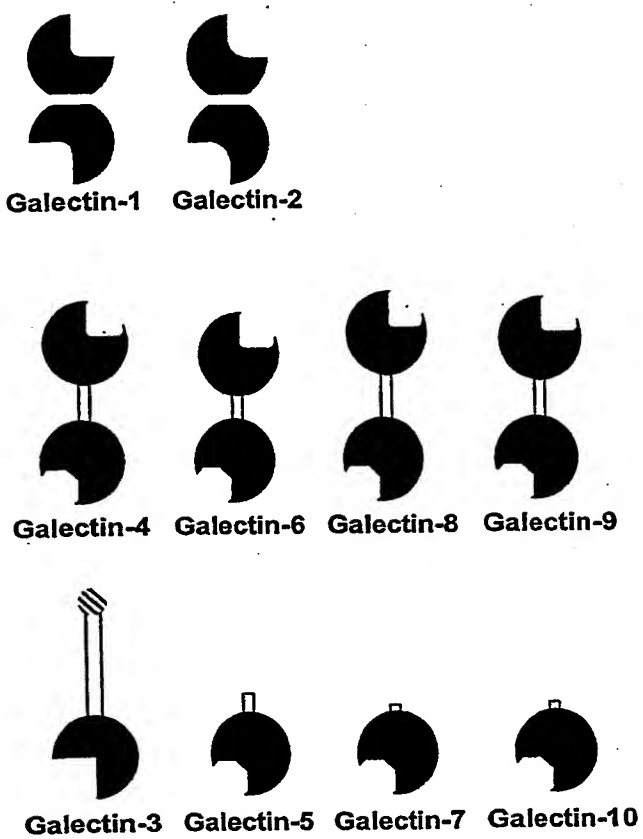
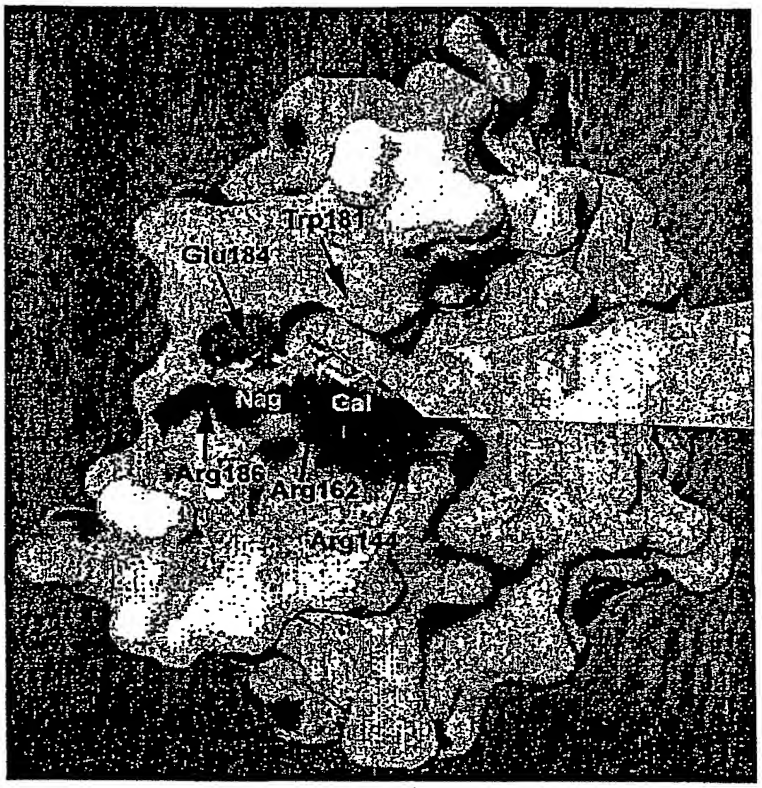

Galectin-1
Galectin-2
Galectin-4
Galectin-6
Galectin-8
Galectin-9
Galectin-3
Galectin-5
Galectin-7
Galectin-10

Fig. 2

A



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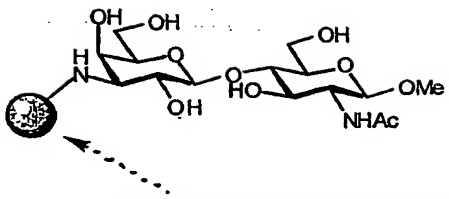
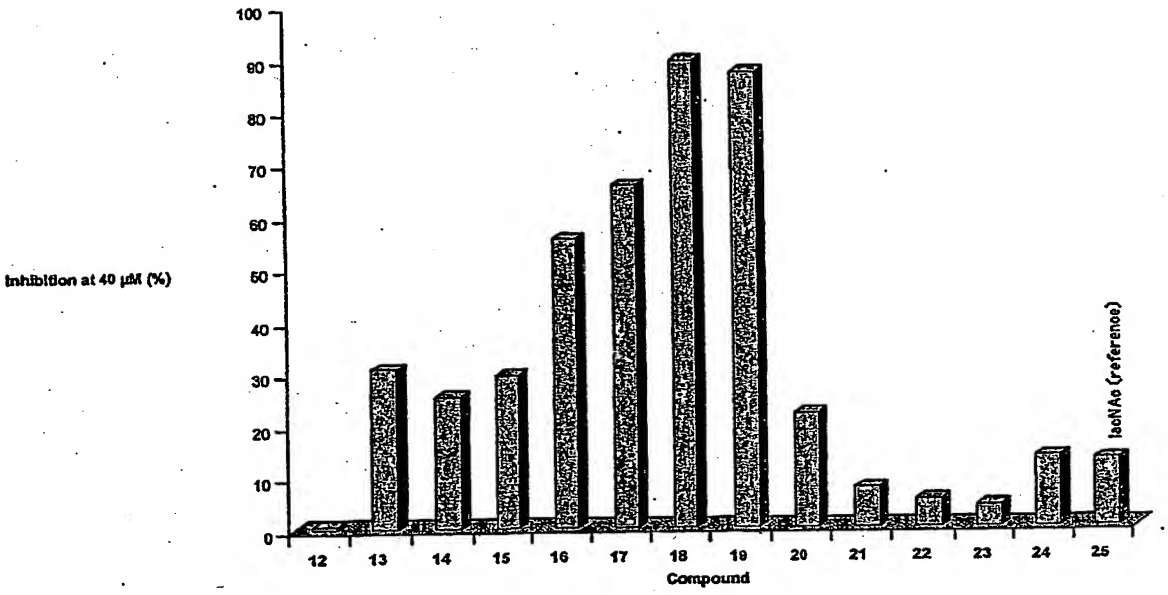
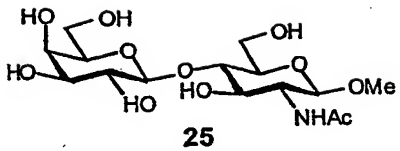


Diverse chemical structures

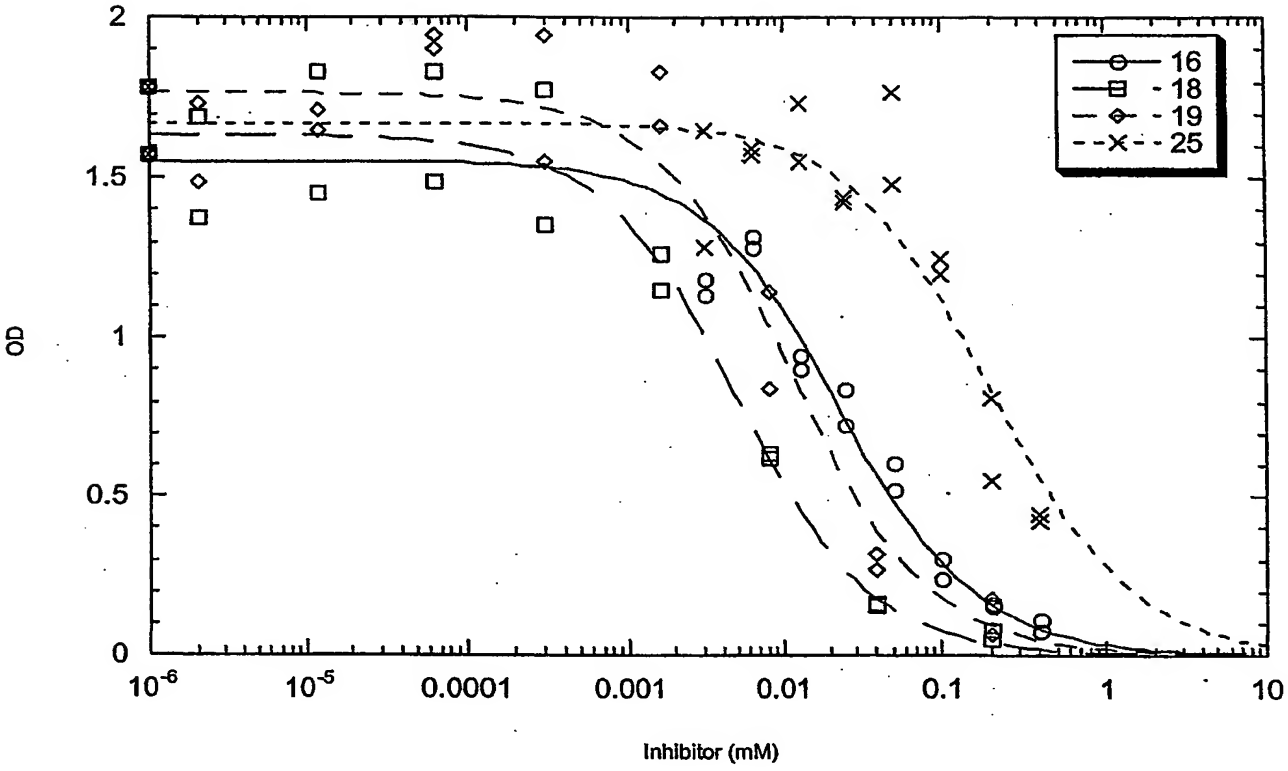
Fig. 3





25
(reference)

Fig. 4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Inhibitor (mM)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00089

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07H 15/12, C07H 5/06, A61K 31/7084, A61P 19/02, A61P 29/00, A61P 35/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07H, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, CHEM.ABS.DATA, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0007624 A2 (TEIJIN LIMITED), 17 February 2000 (17.02.00), see part of page 6 --	1-15
A	WO 0029418 A2 (NOVARTIS AG), 25 May 2000 (25.05.00) --	1-15
A	EP 0561523 A2 (JAPAN TOBACCO INC.), 22 Sept 1993 (22.09.93) --	1-15
A	WO 0017216 A1 (OTSUKA PHARMACEUTICAL CO., LTD.), 30 March 2000 (30.03.00) --	1-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2002	06 -05- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer EVA JOHANSSON/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 02/00089

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	STN International, file CAPLUS, CAPLUS accession no. 1995:902493, document no. 124:117794, Helland, Anne-Charlotte et al: "Methyl 3-amino-3-deoxy-.beta.-D-galactopyranosyl-(1.fwdarw.4)-2-acetamido-2-deoxy-.beta.-D-glucopyranoside: an inhibitor of UDP-D-galactose: .beta.-D-galactopyranosyl-(1-fwdarw.4)-2-acetamido-2-deoxy-D-glucose (1.fwdarw.3)-.alpha.-D-galactopyranosyltransferase & Carbohyd. Res.(1995), 276 (1), 91-8 --	1-15
A	STN International, file CAPLUS, CAPLUS accession no. 1998:539402, document no. 129:288453, Bresalier, Robert S. et al: "Metastasis of human colon cancer is altered by modifying expression of the .beta.-galactoside-binding protein galectin 3", & Gastroenteroloyg, (1998), 115(2), 287-296 -- --------	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE02/00089

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-15
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 13-15 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 02/00089

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0007624 A2	17/02/00	AU 5065399 A	28/02/00
		EP 1104307 A	06/06/01
WO 0029418 A2	25/05/00	AU 1271100 A	05/06/00
		AU 2006399 A	12/07/99
		CA 2315196 A	01/07/99
		US 6292559 B	18/09/01
		US 6317495 B	13/11/01
		WO 9933215 A	01/07/99
		US 6032269 A	29/02/00
		US 6232450 B	15/05/01
EP 0561523 A2	22/09/93	JP 5247078 A	24/09/93
		US 5441932 A	15/08/95
WO 0017216 A1	30/03/00	NONE	

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 July 2002 (25.07.2002)

PCT

(10) International Publication Number
WO 2002/057284 A1

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(21) International Application Number: PCT/SE2002/000089

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0100172-6 22 January 2001 (22.01.2001) SE

(71) Applicants and
(72) Inventors: **NILSSON, Ulf** [SE/SE]; Smedsvovägen 10, S-225 94 Lund (SE). **LEFFLER, Hakon** [SE/SE]; Svanegatan 7 B, S-222 24 Lund (SE). **SÖRME, Pernilla** [SE/SE]; Kulgränden 5B167, S-226 49 Lund (SE).

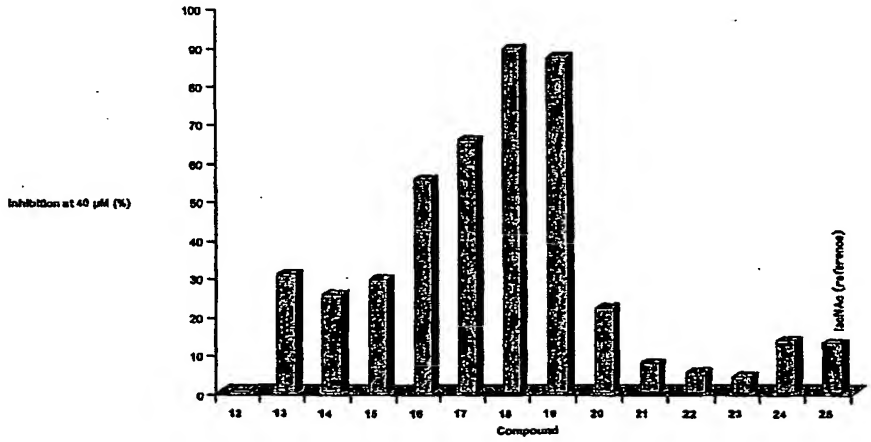
(74) Agents: **AWAPATENT AB** et al.; Box 5117, S-200 71 Malmö (SE).

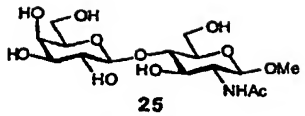
(81) Designated States *(national)*: AE, AG, AL, AM, AT (utility model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (utility model), DE, DK (utility model), DK, DM, DZ, EC, EE (utility model), EE, ES, FI (utility model), FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: NEW INHIBITORS AGAINST GALECTINS





25
(reference)

(57) Abstract: The present invention relates to novel compounds, the use of said compounds as a medicament as well as for the manufacture of a medicament for treatment of disorders relating to the binding of galectin to receptors in a mammal. Said galectin is preferably a galectin 3.

WO 2002/057284 A1

Published:
— *with international search report*

(48) Date of publication of this corrected version:
27 May 2004

(15) Information about Correction:
see PCT Gazette No. 22/2004 of 27 May 2004, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.